CLAIMS

1. An antibody or fragment thereof which is a modified antibody of an inhibitory antibody against FVIII, characterized in that the glycosylation of its variable region has been modified and in that it has substantially the same affinity compared to the native antibody.

2. The antibody or fragment thereof according to claim 1, wherein said modification of the glycosylation is obtained by modulating the glycosylation of an antibody with a conserved N-glycosylation consensus pattern in its variable region.

3. The antibody or fragment thereof according to claim 1, wherein said modification of the glycosylation is obtained by modifying the amino acid sequence of the N-glycosylation consensus sequence in the variable region.

4. The antibody or fragment thereof according to claim 1, wherein said modification of the glycosylation is obtained by the introduction of a glycosylation consensus sequence in the variable region of the antibody.

5. The antibody or fragment thereof of any one of claims 1 to 4, wherein said inhibitory antibody against FVIII is Krix-1.

6. The antibody or fragment thereof according to any of claims 1 to 5 wherein the affinity of said antibody is lower than 1nM.

7. The antibody or fragment thereof according to claim 5, which is KRIX-1Q or KRIX-1A or an scFv fragment, Fab fragment or F(ab')2 fragment of the monoclonal antibody KRIX-1Q or KRIX-1A.

8. The antibody or fragment thereof according to claim 5, wherein the scFv fragment is represented by SEQ ID NO: 26.

9. The antibody or fragment thereof according to claim 5, comprising an immunoglobulin heavy chain comprising an amino acid sequence sequence having at least 70% sequence similarity to SEQ ID NO: 2.

10. The antibody or fragment thereof according to claim 5, comprising an immunoglobulin heavy chain comprising a sequence encoded by a nucleotide sequence having at least 70% sequence identity to SEQ ID No 1.

11. The antibody or fragment thereof according to claim 5, comprising an immunoglobulin light chain comprising an amino acid sequence having at least 70% sequence similarity to SEQ ID No 4.

12. The antibody or fragment thereof according to claim 5, comprising an immunoglobulin light chain comprising a sequence encoded by a nucleotide sequence having at least 70% sequence identity to SEQ ID No 3.

13. A mixture of two or more antibodies or antibody fragments selected from the group consisting of a native inhibitory antibody against FVIII and the modified antibodies according to any one of claims 1 to 12.

14. A pharmaceutical composition comprising the antibodies according to any of claims 1 to 12 or the mixture of claim 13.

15. A method of treatment comprising administering an effective dose of a therapeutic monoclonal antibody or fragment thereof modified in such a way as to modify or introduce a glycosylation site in the antigen binding site of the antibody in order to modify the inhibitory effect of the said antibody on the interaction(s) of the ligand(s) recognized by the said antibody with other proteins or reagents interacting with the said ligand.

16. A method for treatment and prevention of thromboembolic disorders including but not limited to the prevention of deep vein thrombosis and pulmonary embolism secondary to surgical intervention, immobilization or chronic hereditary or acquired thrombophilia, and treatment of deep vein thrombosis, pulmonary embolism, stroke, atrial fibrillation, non Q wave myocardial infarct, non ST elevated myocardial infarct, unstable angina, sepsis or SIRS, comprising administering an effective dose of a monoclonal antibody or fragment thereof according to any of claims 1 to 12 or the mixture of claim 13.

17. A method for treatment and prevention of thromboembolic disorders comprising administering an effective dose of a monoclonal antibody or fragment thereof, according to any one of claims 1 to 12, or the mixture according to claim 13 and administered concomitantly to drug(s) inhibiting platelet aggregation, such as aspirin.

18. A method for treatment of acute myocardial infarct comprising administering an effective dose of a monoclonal antibody or fragment thereof according to any one of claims 1 to 12, or the mixture according to claim 13, and administered concomitantly to drug(s) inhibiting platelet aggregation, such as abciximab (Rheopro^{R}) or antithrombolytic agents (including tissue plasminogen activator, staphylokinase or microplasmin).

19. The method according to any of claims 15 to 18, wherein said monoclonal antibody is an anticoagulant monoclonal antibody derived from Krix-1 and carrying a mutation in the N-glycosylation site of the antigen binding site.

20. A method for obtaining a library of at least two inhibitory antibodies against factor VIII with variable maximal inhibitory activity and with substantially the same affinity, said method comprising modifying the size of an inhibitory antibody against FVIII or fragment thereof by modifying the glycosylation in the variable region of said inhibitory antibody and selecting at least one antibody or fragment for which affinity is not substantially affected.

21. The method of claim 20, which method comprises the step of modifying the glycosylation in the variable region of an inhibitory antibody against FVIII or fragment thereof, and selecting those antibodies for which the affinity is not substantially affected.

22. The method according to claim 20 or 21, wherein said factor VIII inhibitory antibody is directed against the C1 domain of FVIII.

23. The method according to any one of claims 20 to 22, wherein said factor VIII inhibitory antibody is Krix-1.

24. A library of factor VIII inhibitory antibodies obtained by the method according to claim 20 to 23.

25. A method for producing an FVIII inhibitory antibody or fragment thereof said antibody or fragment inhibiting FVIII between 20 and 85 % at saturating concentrations comprising the steps of:

-providing an intact FVIII inhibitory antibody or fragment thereof and,

-modifying the glycosylation of said antibody or antibody fragment at the

posttranslational level or modifying the glycosylation of said antibody or antibody fragment by altering essential amino acids in the glycosylation consensus sequence of the variable region of said antibody

26. A method for the identification of an antibody which competes with an inhibitory FVIII antibody comprising the steps of:
-contacting FVIII or a fragment of FVIII comprising the C1 domain with a first inhibitory antibody and a candidate inhibitory antibody, and
-assaying the capacity of said candidate antibody to compete with the binding of the FVIII inhibitory antibody said FVIII or fragment of FVIII.

27. The method of claim 26 wherein said first inhibitory antibody is Krix-1.

28. The method according to claim 27 further comprising the step of determining the capacity of said second antibody to inhibit FVIII activity.

29. The method according to claim 27 further comprising the step of determining the presence of a partial inhibitory effect on FVIII activity of said second antibody when said second antibody is present at a molar excess.

30. A purified antibody against FVIII which competes with the binding of Krix-1 or a derivative thereof to FVIII, obtainable by the method of according to any of claims 26 to 29.

31. The purified antibody according to claim 30 which is inhibitory for FVIII activity.

32. A mixture of one or more of a purified antibody according to claim 30 or 31 or a derivative thereof, with one or more of a Krix-1 antibody or a derivative thereof, mixed together in an appropriate ratio to achieve a given maximal

inhibition of FVIII activity, whatever the excess of the mixture of antibodies over FVIII.

33. A method for obtaining a library of at least two inhibitory antibodies against factor VIII with variable maximal inhibitory activity and with substantially the same affinity, said method comprising modifying the size of an inhibitory antibody against FVIII either by modifying the glycosylation in the variable region and/or by generating an antibody fragment of said inhibitory antibody and selecting those antibodies or fragments for which affinity is not substantially affected.